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Caries and ABO Secretor Status in a Hungarian Population of Children and Adolescents: An Exploratory Study

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dmf-t/DMF-T · Mixed dentition · Salivary H-antigen secretion

Abstract
ABO blood group antigen (ABGA) secretion into the saliva and other body fluids is a well-known phenomenon, and there is evidence to suggest a link between secretor status and the appearance of caries. It has been proposed that secretion of these antigens into the saliva might be caries-preventive, however, this proposition is still a matter of debate. Our aim was to examine the relationship between caries experience and secretor status in a group of Hungarian children and adolescents in a cross-sectional study. Altogether 130 children and adolescents participated in the study (aged 6–18 years). Participants were divided into two groups according to dentition (i.e. mixed and permanent). ABGA were determined from saliva. The DMF-T and dmf-t (decayed, missing, and filled) indices were calculated, as well as the oral health hygiene index-simplified plaque index. Association of these indices with secretor status was examined. In mixed dentition, the mean dmf-t values were significantly lower in the secretor group (2.1 ± 0.52 SEM), as compared to the nonsecretor group (3.8 ± 0.93 SEM; $p < 0.05$, Mann-Whitney U test). The finding that children of mixed dentition are apparently better protected against caries suggests that the assumed protective effect might be associated with deciduous teeth, but given the general paucity of knowledge about this topic, further research is indicated.

ABO blood group antigens (ABGA) are an integral part of the red cell membrane, and are also expressed into the body fluids. The ABO system, discovered by Landsteiner [1901] in 1901, is based on the modifications of the H antigen, a carbohydrate sequence, which, when present on the surface of erythrocytes in its unmodified form, codes the O type. The A, B and AB types are coded by addition of α-N-acetylgalactosamine and α-D-galactose to the H chain [Takizawa et al., 2000]. About 70–80% of the population secretes ABGA in the saliva and other body fluids where these antigens are bound primarily to mucins [Wolf and Taylor, 1964; Arneberg et al., 1976; Vidas et al., 1999]. Based on whether an individual secretes ABGA into body fluids, secretors and nonsecretors are differentiated between, which is defined

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as secretor status. The secretor status depends on which alleles for the Lewis antigen system the individual carries, that is, an individual carrying the dominant Le and Se alleles will be a secretor [Grubb, 1948; Simmons et al., 1951]. The percentage of secretors in Caucasian populations has been approximated at 80% [Wolf and Taylor, 1964]. As pointed out by Vidas et al. [1999], the secretor status of a patient may possibly be a factor influencing the development of systemic oral disease. According to Demir et al. [2007], the ABO blood subgroups and the Rh factor may constitute a risk factor in the development of periodontal diseases. The authors found a relatively higher percentage of A group patients in their gingivitis group and a relatively higher percentage of O group patients in their periodontitis group. Other studies reached different conclusions. For instance, it was found that the prevalence of vaginal candidiasis was significantly higher in nonsecretors [Kulkarni and Venkatesh, 2004]. McGovern et al. [2010] found the fucosyltransferase 2 nonsecretor status to be associated with Crohn's disease. Sakamoto et al. [1976] found no association between DMF (decayed, missing, and filled teeth) scores and either β-glucuronidase inhibitor activity or secretor status. A seminal Icelandic study suggested that blood group antigens may interfere with the adherence of *Streptococcus mutans* to teeth, thereby having a preventive effect against caries [Holbrook and Blackwell, 1989]. Still other studies revealed a connection between certain diseases and secretor status, including myocardial infarction [Nydegger et al., 2003], transitional cell carcinoma of the bladder [Chihara et al., 2005] and pancreatic cancer [Risch, 2012]. The aim of the present study was to investigate the hypothesized effect of ABGA expression into saliva on caries in a group of Hungarian children and adolescents. The primary aim was to examine if caries experience might be associated with secretor status in this population. It is important to emphasize that this study – to our knowledge the first to address this specific issue – was designed as exploratory, and therefore results are to be interpreted as preliminary.

Materials and Methods

Study Population

The study was carried out at the dentistry clinic of the Faculty of Dentistry of the University of Szeged in 2011. A sample of 130 healthy schoolchildren (children and adolescents aged between 6 and 18 years, $n_{male} = 60$, $n_{female} = 70$) present for an annually organized screening participated in this study. The sample size was determined by the turnup rate (annual screening is not mandatory in Hungary), willingness to participate, and the exclusion criteria. Only healthy subjects with no known oral or systemic disease were eligible for the study. Taking any kind of medication per os at the time of saliva sampling was also an exclusion criterion. However, to assure that the resulting sample size yielded statistically meaningful results, a post hoc power analysis was conducted (see 'Results'). The participants were all Caucasian of a homogeneous socioeconomic background. The study protocol conformed to the tenets of the Declaration of Helsinki in all respects, and it was approved by the Ethical Board of the University of Szeged. Participants and their parents were provided information regarding the goals, risks and the procedures involved in the study in both oral and written form. Upon receiving this information, the parents of the participants were asked to give their consent to the participation of their children by signing an informed consent form.

Caries Experience and Oral Hygiene

Data for the calculation of dmf-t/DMF-T were collected as part of a routine dental status assessment. Caries experience was assessed by calculating the dmf-t/DMF-T scores according to the WHO criteria. A tooth with more than one carious lesion was scored as one decayed tooth; a tooth with a filling and a separate carious lesion was scored as one filled tooth. The simplified oral health hygiene index (OHI-S) was also calculated [Greene and Vermillion, 1964]. These calculations were carried out prior to secretor status determination, therefore, the dentist performing the assessment was blind to subjects' secretor status.

Secretor Status and ABO Blood Group Determination

Secretor status was determined along the lines described in Vidas et al. [1999]. Unstimulated whole saliva (3–4 ml) was collected from each subject. Saliva collection took place either in the morning hours or early in the afternoon, but at least 2 h after the last meal or toothbrushing. Saliva was collected in test tubes. A glass funnel with a piece of absorbent paper inside it was inserted into the test tube, and participants were asked to spit into the funnel 1 or 2 times per minute. Using this procedure it was possible to collect an average of 3–4 ml of saliva. The absorbent paper inside the funnel served to filter contaminants.

Samples collected this way were sealed and placed in boiling water for 10–20 min to inactivate the enzymes. Samples were then centrifuged at 3,000 rpm for 5 min and the supernatant was separated and analyzed for ABGA (the saliva samples were either processed immediately or stored at –80°C until use) by a hemagglutination inhibition test with appropriate antisera (Blood Grouping Test Reagents Anti-A, Anti-B, Anti-H, Sifin® Berlin, Germany; ALBA clone Anti-A, Anti-B, Anti-H Blood Grouping Reagents, Alba Bioscience®, Edinburgh, United Kingdom). A plate hemagglutination-inhibition test was employed in the following manner: the saliva samples were diluted in a ratio of 1:2, while A-, B-, and H-antisera were diluted in a ratio of 1:8. Sterile distilled water was used for dilution. The diluted saliva samples and antisera were then mixed in test tubes and stored in a wet chamber for 10 min. After the incubation period, 1–2 drops of 2–3% erythrocyte solution were added to each, and the result was recorded. The hemagglutination reaction indicated a lack of ABO antigen production, and a reaction not taking place revealed the presence of antigens in the saliva samples, as in the latter case the antigen-antibody complexes were already formed when the proper antiserum was added to the saliva sample. In the case of nonsecretors no reaction was seen.

Table 1. Descriptive statistics of the sample

	Gender ratio F:M	Mean age, years (range)	Mean OHI-S (range)	Mean dmf-t (range)	Type A, %	Type B, %	Type AB, %	Type O, %
Secretor								
Mixed dentition (n = 41) (Caries-free: 51.16%)	23:18	9.56 (6–12)	0.97 (0–2.6)	2.02 (0–13)	48.8	14.6	17.1	19.5
Permanent dentition (n = 54) (Caries-free: 46.67%)	32:22	15.8 (14–18)	0.81 (0–3.2)	2.43 (0–12)	42.6	20.4	14.8	22.2
Nonsecretor								
Mixed dentition (n = 18) (Caries-free: 25%)	4:14	9.72 (7–12)	1.19 (0–2.5)	3.61 (0–13)	N/A	N/A	N/A	N/A
Permanent dentition (n = 17) (Caries-free: 38.46%)	11:6	15.05 (13–18)	0.87 (0–2.5)	3.1 (0–11)	N/A	N/A	N/A	N/A

N/A = Not applicable.

Statistical Analysis

The study population was divided into two groups on the basis of dentition (i.e. mixed or permanent), within which secretor and nonsecretor subgroups were determined. Data analysis was conducted on the basis of this grouping. The mixed dentition group had both deciduous and permanent teeth, the permanent dentition group had permanent teeth only.

Data were analyzed using SPSS 17.0 software. As our data did not fulfill the normal distribution criterion, we used the nonparametric Mann-Whitney U (MWU) test for between-group comparisons. To determine the degree of association between dmf-t/DMF-T and OHI-S, the χ^2 test was used. Wherever our dataset violated the assumption of the χ^2 test (i.e. expected frequencies of at least five), we used Fisher's exact test. The level of significance was $p < 0.05$. Post hoc power analysis for the dmf/DMF comparisons was conducted in G*Power (Universität Kiel, Germany).

Results

Basic Statistics

Data were analyzed by dentition type and secretor status. Of the 130 subjects, 95 (73%) turned out to be secretors, of which 54 (56.8%) had permanent dentition (mean age: 15.63 years; range: 14–18 years) and 41 (43.2%) had mixed dentition (mean age: 9.86 years; range: 6–13 years). Of the 35 (26.9%) nonsecretors 17 (48.6%) had permanent dentition and 18 (51.4%) had mixed dentition. In both dentition types approximately 40% of the subjects were caries-free (defined as dmf-t/DMF-T = 0), however, the ratios differed considerably by secretor status (table 1). The ratio of secretors to nonsecretors was in accordance with previously published data (see introduction). ABO antigen distribution in secretors was also determined from the 130 samples of saliva. The distribution for the whole examined secretor population was as follows: A 44.2%, B 16.8%, AB 15.8%, O 23.2%. Detailed basic statistics by dentition and secretor status are given in table 1.

Association between OHI-S and dmf-t/DMF-T

The association between OHI-S and dmf-t in mixed dentition was not significant, while between OHI-S and DMF-T in permanent dentition significant association was found: χ^2 (252, n = 71) = 346.93, p = 0.000.

Comparison of DMF-T/dmf-t between Secretors and Nonsecretors

There was no statistically significant difference in DMF-T status between secretors and nonsecretors in permanent dentition ($n_1 = 17$, $n_2 = 54$, U = 454.5, p = 0.952, MWU). However, statistically significant difference was found in dmf-t between secretor and nonsecretor statuses in mixed dentition ($n_1 = 18$, $n_2 = 41$, U = 234, $p < 0.05$, MWU). Post hoc power analysis revealed a high statistical power: $1 - \beta = 0.89$ ($d = 0.5$, $\alpha = 0.05$). To determine if this effect was linked to any particular secreted antigen, association between dmf-t and antigen types was computed, but no significant association was found: χ^2 (30, n = 41) = 23.16, p = 0.809. A graphical representation of the comparisons is given in figure 1. In particular, the mean (±SD) dmf-t values in mixed dentition were significantly lower in the secretor group (2.1 ± 3.46) compared to the nonsecretor group (3.8 ± 3.94). When only dentition types were compared, without taking secretor status into account, this difference disappeared (2.60 ± 3.76, 2.59 ± 3.13, mixed and permanent, respectively; mean ± SD).

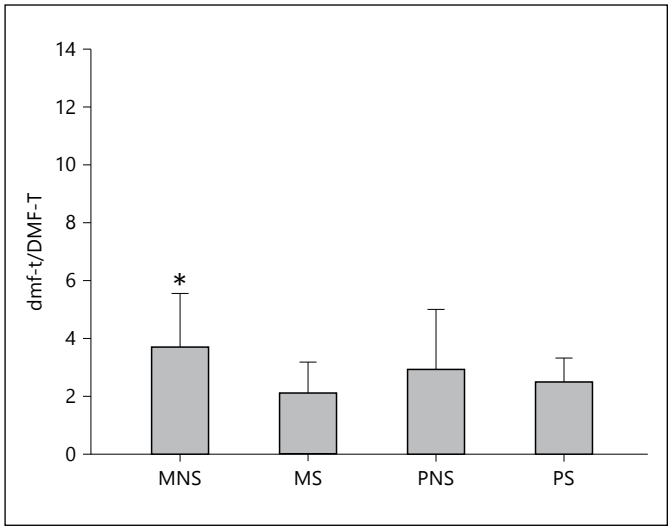

Fig. 1. Comparison of dmf-t/DMF-T by dentition type and secretor status. MNS = Mixed, nonsecretor; MS = mixed, secretor; PNS = permanent, nonsecretor; PS = permanent, secretor. Bars denote means, whiskers mark 95% CI. Significant difference: * $p < 0.05$. For details see 'Results'.

Sex Differences

Significant sex difference was found only in the mixed dentition group ($n_1 = 33$, $n_2 = 30$, $U = 322$, $p = 0.017$, MWU). This means that at an average, girls between 6 and 12 years exhibited better oral hygiene as measurable by OHI-S than boys of the same cohort (mean OHI-S 0.83 vs. 1.21, respectively). In the permanent dentition group no such difference was seen ($n_1 = 27$, $n_2 = 40$, $U = 393$, $p = 0.061$, MWU). The association between sex and secretor status in mixed dentition was significant ($p = 0.000$, Fisher's exact test), while in permanent dentition no significant association was found ($p = 0.458$, Fisher's exact test). To verify that the DMF-T/dmf-t comparisons were not influenced by different oral hygiene as related to sex, we also compared OHI-S between the sex subgroups of the secretor/nonsecretor groups. No significant difference was found for either sex (secretors vs. nonsecretors, girls: $n_1 = 54$, $n_2 = 15$, $U = 397$, $p = 0.914$, MWU; boys: $n_1 = 39$, $n_2 = 20$, $U = 345$, $p = 0.479$, MWU).

Discussion

Although association has been suggested with a number of diseases, a relatively small number of studies dealt with the possible association between ABO secretor status and dental caries in humans, especially in children and adolescents. Whether ABO secretor status influences dental caries is yet to be determined.

Mavridis and Achimastos [1974] found higher mean DMF-T in secretors, the difference, however, was not significant. Barros and Witkop [1963] found no relation between DMF-T and ABO and MN blood groups in a large Chilean population, while Arneberg et al. [1976] found lower caries prevalence for secretors, regardless of blood group, with a more pronounced difference for smooth surfaces (i.e. oral or vestibular tooth surfaces). Studying a population of young Icelanders, Holbrook and Blackwell [1989] found significantly lower DMF in secretors than nonsecretors. The authors suggested that blood group antigens may interfere with the adherence of *S. mutans* to teeth [Holbrook and Blackwell, 1989]. It is to be noted that in Iceland the proportion of nonsecretors is among the highest recorded in Europe [Eriksson et al., 1986], and the prevalence of caries, especially in childhood, is accordingly high [Agustsdottir et al., 2010], which seems to be a strong argument for the protective role of ABO secretion. Still other studies [Green et al., 1966; Achimastos et al., 1974] failed to confirm an association of caries experience and ABO secretion.

Our present study, in which we examined a sample of 130 children and adolescents in order to identify if an association exists between caries experience and secretor status, might be regarded as an addition to this debate.

The only significant, secretor status-related difference was found in dmf-t which was significantly higher in nonsecretors, which is the main finding of our study. Significant sex difference was also found in oral hygiene in the mixed dentition group, however, no association was found between dmf-t/DMF-T and OHI-S in either group.

This latter result, counterintuitive as it may seem, is not problematic, because oral hygiene per se is obviously not the only factor influencing caries formation. We assume that OHI-S may be a sensitive predictor of caries status only in poor oral hygiene. Matulaitiene et al. [2012] examined oral health indices of Lithuanian schoolchildren of average to good oral hygiene, and reported that while dmf-t/DMF-T decreased significantly in the studied period (1983–2009), OHI-S did not reflect this change.

The significant sex difference in the younger (mixed dentition) group is also understandable, in light of the superiority of girls over boys in terms of oral hygiene in this cohort [Al Dosari et al., 2000; Kolawole et al., 2011]. The explanation of this, however, is beyond the scope of this article.

The main finding of our study, that is, that ABO secretors of mixed dentition exhibit lower caries experience, is

rather difficult to explain at the present level of our knowledge, especially considering that studies focusing on ABO secretion and caries in children are limited. Our results definitely show that this effect is associated with mixed dentition, that is, the presence of primary teeth. Considering that primary teeth are more caries-prone due to the lower mineral content of their enamel layer [Wilson and Beynon, 1989], their morphology [Sabel, 2012], and narrow interdental spaces [Warren et al., 2003], it might be hypothesized that secretion of ABO antigens into the saliva may provide some sort of extra protection to primary teeth. In this respect it is important to note that tooth surface was found to be a significant factor in another study dealing with secretor status and caries experience too [Arneberg et al., 1976]. Our findings, of course, and especially in view of the Icelandic sample [Holbrook and Blackwell, 1989], do not necessarily imply that the hypothesized preventive effect is completely missing in adulthood. We would argue, rather, that it is more remarkable when the more vulnerable deciduous teeth are still present.

The exploratory nature of this study naturally raises the issue of whether the observed effect could be due to some uncontrolled background variable, such as dietary or oral hygiene differences between the cohorts. No direct measurements were done to address such variables, obviously a limitation of the study. However, the fact that the significant dmf-t/DMFT difference between the dentition types was seen only when secretor status was considered as an influencing factor, seems not to support such a scenario. Furthermore, no significant difference in OHI-S as a measure of oral hygiene was found between the dentition type-based cohorts (mixed: 2.59 ± 3.67, permanent: 2.60 ± 3.13; mean ± SD), which makes it quite unlikely that significant changes of oral hygiene habits occurred with age.

As the influence of secretor status on caries experience has been paid surprisingly little attention since the 1970s when the subject was first mentioned, the exact protective mechanism remains unknown. Based on the available literature it is possible to set up a reasonable explanatory framework, however, it must be noted that this framework – due to the paucity of research into these mechanisms – can only be speculative in nature. Our proposed explanation focuses on salivary glycoproteins (mucins) and their role in bacterial attachment.

As a starting point we hypothesize that the observed protective effect is due to ABO antigens' interference with the attachment of cariogenic bacteria to the surface of the teeth. This hypothesis was articulated earlier [Holbrook and Blackwell, 1989] in connection with *S. mutans*, but the authors did not put it in detail. It must be also noted that several other species have been shown to play a role in caries formation and progression [Aas et al., 2008].

Williams and Gibbons [1975] observed that mucinous glycoproteins could aggregate certain bacterial species and prevent them from attachment to the buccal epithelium. The authors suggested that this was possible through a kind of molecular mimicry, that is, mucinous glycoproteins possessed antigenic determinants in common with a wide range of body cells (including those of the buccal epithelium), and it was these antigenic determinants by which the glycoproteins could aggregate bacteria. More importantly, it was also shown that pretreatment of epithelial cells from a donor of A blood type with A antiserum prevented the attachment of *Streptococcus sanguis* to these cells. This finding supported the theory that blood group antigens could establish a link between bacteria and the surface on which they are located. However, the study focused on the buccal epithelium, not the solid hydroxyapatite surface of teeth, and no testing was done to find out about if mucin donors were secretors or not, so the results are best interpreted as characterizing salivary mucins in general. The key finding of the study, therefore, is possibly that salivary mucins are able to aggregate bacteria, which, however, is not a really promising finding in terms of caries protection.

Mucins are crucial components of the acquired enamel pellicle without which bacteria could not colonize tooth surfaces and form a complex biofilm, the metabolic processes of which lead to caries, gingivitis and periodontitis. The acquired pellicle is composed of a variety of salivary glycoproteins and antibodies. This film alters the characteristics of the surface, which in turn increases the efficiency of bacterial adhesion [Lang et al., 2008]. That is, the aggregation of bacteria by mucins in the enamel pellicle is a pro-caries process, and therefore it cannot account for the protection observed in ABO secretors. How then do mucins play a role in protection? ABO antigen determinants in secretors are located at the terminal part of the carbohydrate side chain in glycoproteins of the mucin type [Marcus, 1969]. In other words, the mucins of secretors are structurally different. We hypothesize that this structural difference might play a key role in the protective effect. Bacteria invade the pellicle-coated enamel surface as primary and secondary colonizers. Primary colonizers (like *S. mutans*) attach directly to the glycoproteins of the acquired pellicle, while secondary colonizers attach to the primary ones [Lang et al., 2008]. On such premises we suggest that two explanations are possible.

One is that the structural difference of the mucins of secretors deteriorates their ability to aggregate cariogenic bacteria. The finding that pretreatment of mucins with anti-ABO antisera did not influence their ability to aggregate *Streptococcus miteor* [Williams and Gibbons, 1975] might be a counterargument here, but by no means an unquestionable one, as the secretor status of mucin donors was not known, and the effect was found to be species-dependent, even at a very low number of studied species (*S. miteor, S. sanguis and Streptococcus salivarius*). This latter finding suggests high interspecies variability. The other explanation may be that structurally altered (secretor) mucins do not adhere so readily and stable to the enamel surface as nonsecretor mucins, therefore, they cannot serve as a firm base for colonization. In any of these two scenarios, part of the maximal adhesive surface would be lost, and colonization would be less efficient. This would mean much better but still not perfect caries resistance, as there are several known cariogenic species, and, as mentioned before, the effect appears to be species-dependent. The results of this study and those of other studies suggesting that secretors are better protected but not completely caries-free correspond to such a scenario.

To our knowledge, this is the first study to address the relationship between secretor status and caries experience in school-age children by dentition type. Our results corroborate other studies that found ABO antigen secretion protective against caries. What is novel about these results is that they raise the possibility that salivary ABO secretion might play a role in the protection of primary teeth, but to confirm this finding further research is necessary, especially regarding the background mechanisms.

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Disclosure Statement

The authors declare no conflict of interest.

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